Structurally Simple Trichostatin A-Like Straight Chain Hydroxamates as Potent Histone Deacetylase Inhibitors

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A series of new, structurally simple trichostatin A (TSA)-like straight chain hydroxamates were prepared and evaluated for their ability to inhibit partially purified human histone deacetylase 1 (HDAC-1). Some of these compounds such as **8m**, **8n**, **12**, and **15b** exhibited potent HDAC inhibitory activity with low nanomolar IC_{50} values, comparable to natural TSA. These compounds induce hyperacetylation of histones in T24 human cancer cells and significantly inhibit proliferation in various human cancer cells. They also induce expression of p21 and cause cell cycle blocks in human cancer cells. In this paper, we describe the synthesis of these new compounds as well as structure−activity relationship results from enzyme inhibition and alterations in cellular function.

Introduction

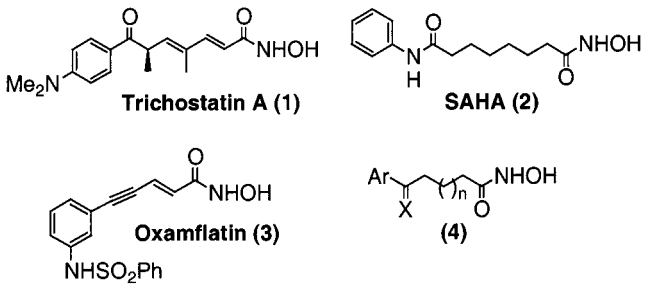
Histone acetylases (HATs) and histone deacetylases (HDACs) are a group of enzymes that catalyze acetylation and deacetylation of lysine residues in the N-terminal tails of core histones.[1] HDACs were identified as transcriptional corepressors by restricting the accessibility of a variety of transcription factors to DNA and by mediating changes in nucleosome conformation.[2] Inhibition of HDAC activity represents a novel approach for intervening in cell cycle regulation; thus, HDAC inhibitors could have great therapeutic potential in the treatment of cell proliferative diseases.[3] Several small molecule inhibitors of HDAC, such as the natural product trichostatin A (TSA)[4] **1** (Chart 1), the synthetic compounds suberoylanilide hydroxamic acid (SAHA)[5] **2**, and oxamflatin [6] **3**, have been reported to induce differentiation of several cancer cell lines and to suppress cell proliferation.[7]

As part of our efforts to discover novel HDAC inhibitors,[8] we prepared a series of structurally simple TSA-like straight chain hydroxamate analogues of **4**, with varying chain lengths, aryl substitutions, and aryl-aliphatic chain connections (e.g., ketone, alkene, oxime, etc). We now report the synthesis of these new compounds and the resulting structure−activity relationships (SAR) for HDAC inhibition and alterations in cellular function.

Chemistry

To prepare new TSA-like straight chain hydroxamic acid derivatives of type **4** having various chain lengths, aryl substitutions, and aryl-aliphatic chain connections, we chose a general synthetic strategy as outlined in Scheme 1.

Chart 1



Our synthesis began with the coupling of the readily available copper reagent **6**, derived from ethyl 7-bromoheptanoate **5**, with aryl and heteroaryl acid chlorides to afford a variety of aryl ketoesters of type **7**. Aryl ketoesters **7** served as convenient intermediates for many of the hydroxamates described herein. The Suzuki coupling of **7** (Ar = *p*-Br-phenyl) with a variety of aryl boronic acids of choice provided various biphenyl derivatives **11**. A variety of amino-substituted phenyl ketoesters **14** could be also accessed by palladium-catalyzed amination of **7** (Ar = *p*-Br-phenyl). Hydrolysis of aryl ketoesters (**7**, **11**, and **14**) and subsequent coupling of the resulting carboxylic acids with hydroxylamine (1 equiv) under a typical peptide coupling condition (EDC/HOBt) gave their respective aryl ketone hydroxamates **8**, **12**, and **15**. Hydroxamic acids **9** bearing an oxime moiety instead of a ketone were prepared in a similar manner but using an excess of hydroxylamine. Aryl oxime carboxylic acid **13** could also be prepared by reacting the corresponding aryl ketone carboxylic acid with hydroxylamine in pyridine. Wittig reaction of **7** with methyl triphenylphosphonium bromide followed by the same two step transformation described above afforded the desired olefinic hydroxamate **10**. The α-methylated hydroxamic acid **16** was prepared from **7** (Ar = 2-naphthyl) in order to evaluate the steric tolerance around the Zn-chelating hydroxamate moiety.

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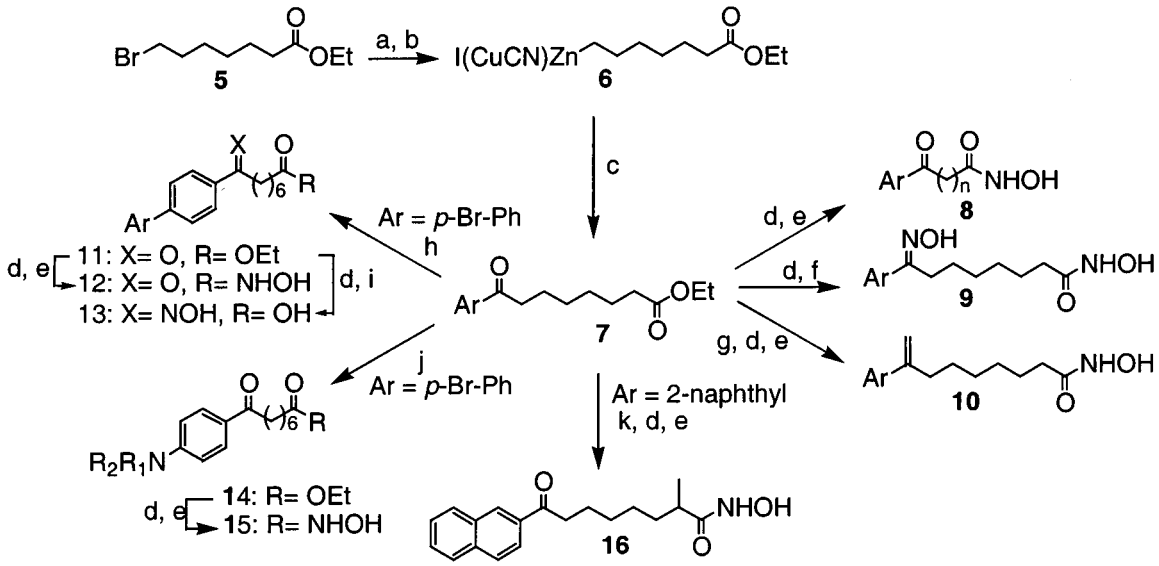
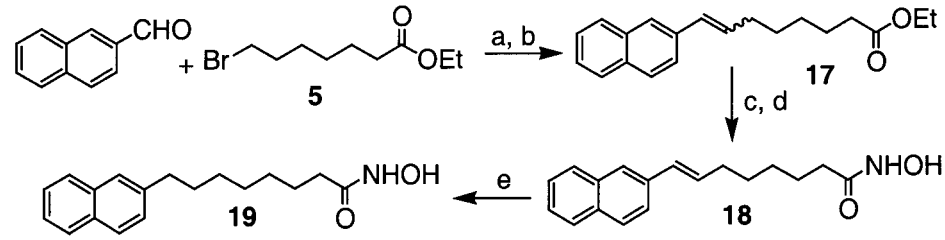
Scheme 1[a]



[a] Conditions: (a) NaI, acetone, reflux, 83%. (b) (i) Zn, $(CH_2)_2Br_2$, TMSCl, THF; (ii) LiCl, CuCN, reflux. (c) ArCOCl, THF, 0 °C. (d) 1 N NaOH, THF−MeOH. (e) EDC, HOBt, $NH_2OH·HCl$ (1.1 equiv), Et_3N. (f) EDC, HOBt, $NH_2OH·HCl$ (5 equiv), Et_3N. (g) $CH_3PPh_3^+Br^-$, *n*-BuLi, THF. (h) $ArB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene, 100 °C. (k) (i) $HO(CH_2)_2OH$, $BF_3·OEt_2$, $HC(OCH_3)_3$, CH_2Cl_2, 44%; (ii) LDA, CH_3I, THF, 91%; (iii) 1 N HCl, acetone, 50 °C.

Scheme 2[a]



[a] Conditions: (a) PPh_3, toluene, 87%. (b) *n*-BuLi, THF, and then 2-naphthaldehyde, 34%. (c) 1 N NaOH, THF−MeOH, 60%. (d) EDC, HOBt, $NH_2OH·HCl$ (1.1 equiv), Et_3N, 37%. (e) H_2, Pd/C, MeOH, 97%.

Protection of the ketone as a cyclic ketal followed by α-methylation of the ester group, using methyl iodide and LDA as a base, furnished the α-methylated ester. Acidic hydrolysis of the cyclic ketal and hydroxamate formation as described above allowed the preparation of hydroxamate **16**.

Finally, hydroxamates **18** and **19** (Scheme 2) were readily prepared from ester **17**, which in turn was obtained from a Wittig reaction of 2-naphthylaldehyde and the phosphonium ylide derived from ethyl 7-bromoheptanoate **5**. Subsequent catalytic hydrogenation of the alkene group in **18** gave the 2-naphthyl-alkylhydroxamic acid **19**.

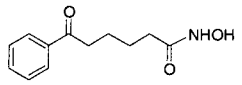
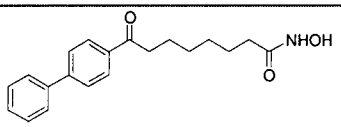
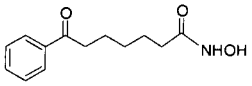
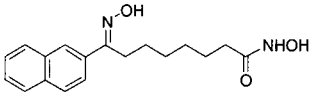
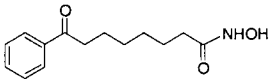
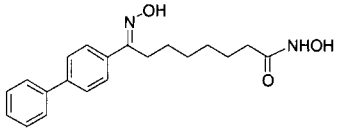
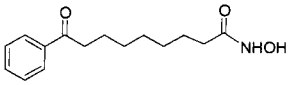
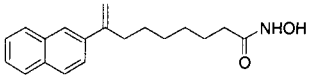
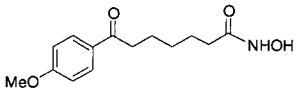
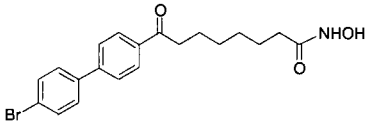
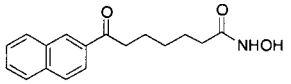
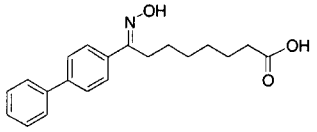
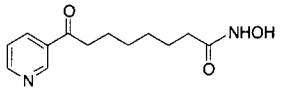
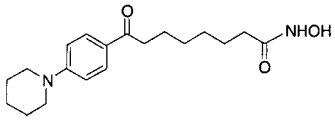
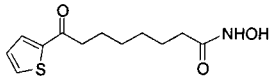
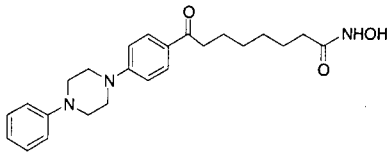
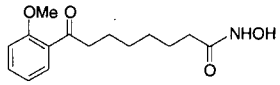
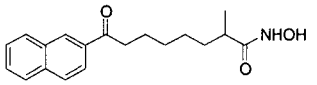
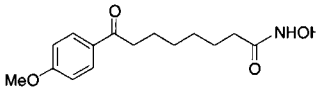
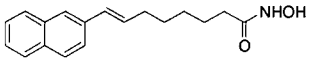
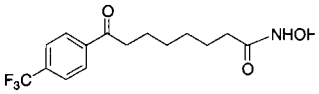
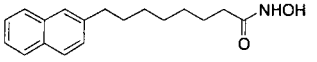
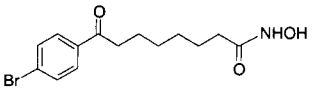
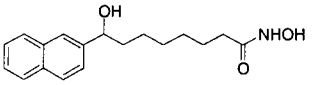
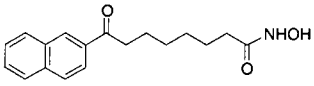
SAR and Biological Results

Enzyme Inhibition. All compounds were tested in vitro for the inhibition of recombinant human HDAC-1.[9] We chose HDAC-1 since this isozyme has been widely implicated in both transcriptional repression and chromatin remodeling. The IC_{50} values for some representative hydroxamates prepared are shown in Table 1.

Chain Length. X-ray crystallographic studies using the HDLP−TSA complex have shown that TSA binds by inserting its long aliphatic chain into the tubelike active site pocket, thus allowing the hydroxamate group to chelate with the zinc ion and active site residues.[10] The aryl portion may act as a cap to bind the molecule at the rim of the pocket and into an adjacent surface groove. For rapid SAR development, we first prepared a series of hydroxamates with different chain lengths (4−7) between the hydroxamate-carbonyl and aryl ketone group and evaluated their inhibition using HDAC-1. Hydroxamate analogues with a chain length of six carbons were most effective; hydroxamate analogues with either shorter (**8a**,**b**) or longer carbon chain lengths (**8d**) were much less effective in an order of 6 > 7 > 5 > 4 carbon length. The importance of the carbon chain length in enzyme inhibition can be seen more drastically in two *p*-methoxyphenyl hydroxamates, **8e**,**j**, as well as in two 2-naphthyl hydroxamates, **8f**,**m**. Analogue **8j** with a six carbon chain is a strong inhibitor of the enzyme with an IC_{50} of 15 nM, whereas the analogue with a five carbon chain **8e** has 30-fold weaker inhibitory activity, with an IC_{50} of 450 nM. These results suggest that our hydroxamate-based inhibitors with the optimal six carbon methylene spacer may fit well in the narrow, tubelike, hydrophobic portion of the active site and make multiple van der Waals contacts. Thus, like TSA, these inhibitors probably mimic acetylated lysine, the natural substrate of core histone proteins.[9]

Substitution on the Aryl Group. After the optimal carbon chain length was established, we next examined

Table 1. HDAC-1 Inhibitory Activities

Cpds	Structures	HDAC-1 IC_{50}, nM[a]	Cpds	Structures	HDAC-1 IC_{50}, nM[a]
8a		1500 ± 500	**8n**		5 ± 1
8b		500 ± 100	**9a**		8.5 ± 1.5
8c		65 ± 5	**9b**		4 ± 0.1
8d		135 ± 65	**10**		8 ± 1
8e		450 ± 150	**12**		2 ± 1
8f		35 ± 5	**13**		200 ± 100
8g		153 ± 93	**15a**		9.5 ± 0.5
8h		50 ± 20	**15b**		4.5 ± 1.5
8i		95 ± 5	**16**		600 ± 100
8j		15 ± 5	**18**		6 ± 1
8k		45 ± 15	**19**		25 ± 15
8l		45 ± 15	**20**		35 ± 15
8m		5 ± 1		trichostatin A	5 ± 0.1

[a] Values are means of three separate experiments ± standard deviation (SD).

the effect of substitution on the aryl group. Several observations arise from examination of IC_{50} data from Table 1: (i) an ortho-methoxy substitutent, as in **8i**, does not improve enzyme inhibition relative to the nonsubstituted analogue **8c**, whereas the corresponding para-methoxy analogue **8j** is 4−5 times more potent than **8c**; (ii) an electron-withdrawing substituent, *p*-trifluoromethyl or *p*-bromo, has little effect on enzyme inhibitory activity (cf. **8k**,**l** as compared to **8c**); (iii) the introduction of an additional hydrophobic aryl group as in **8m**,**n** and **12** enhances enzyme inhibitory activity significantly. The most potent HDAC inhibitor in the present series is the *p*-bromo biphenyl hydroxamate **12** with an IC_{50} of 2 nM, as compared to the 5 nM IC_{50} value for natural TSA. It is noteworthy that none of the parent aryl ketone carboxylic acids are active but that the biphenyl

Table 2. Inhibition of Cell Proliferation (MTT Assays) of **8m**, **8n**, **12**, and **15b** in Human Normal and Cancer Cells[a]

compds	T24	HCT 116	SW48	A549	H446	DU145	MDAmb 231	MCF-7	HMEC
TSA	0.15 ± 0.05	<0.05	0.1 ± 0.01	0.16 ± 0.04	0.08 ± 0.02	0.2 ± 0.1	0.09 ± 0.01	0.1 ± 0.01	1.6 ± 0.4
8m	17 ± 4	1.5 ± 0.5	6.5 ± 1.5	29 ± 8	1.5 ± 0.5	29 ± 8	0.95 ± 0.05	25 ± 2	4 ± 1
8n	1 ± 0.1	4.5 ± 0.5	1.5 ± 0.5	1 ± 0.1	0.65 ± 0.15	0.9 ± 0.1	0.6 ± 0.2	2 ± 1	2 ± 1
12	0.8 ± 0.02	0.7 ± 0.2	3 ± 0.1	0.3 ± 0.05	0.7 ± 0.2	1 ± 0.1	0.05 ± 0.01	3 ± 0.5	7 ± 0.5
15b	7 ± 1	4 ± 0.1	2.5 ± 0.5	5 ± 1	1 ± 0.1	5.5 ± 0.5	0.8 ± 0.2	2 ± 1	>20

[a] Substance concentration (μM) required to reduce tumor cell growth by 50%.

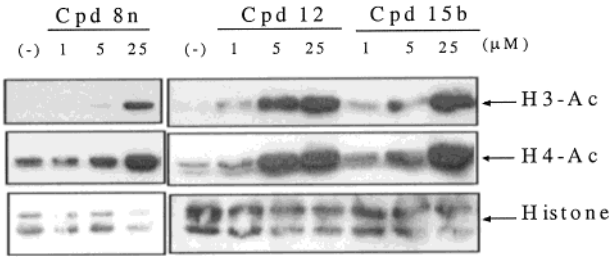


Figure 1. Histone H3 and H4 acetylation in human bladder cancer T24 cells induced by compounds **8n**, **12**, and **15b**. Histones were extracted from T24 cells that had been exposed to **8n**, **12**, and **15b** at 0, 1, 5, and 25 μM for 16 h and analyzed by Western blot with antibodies specific for either acetylated H4 or acetylated H3 histones. The bottom panel (coomassie staining of the gels) indicates the loading of histones.

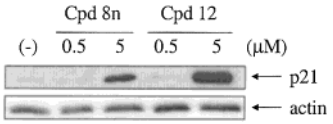


Figure 2. Induction of p21 expresssion by HDAC Inhibitors. Human bladder carcinoma T24 cells were treated with 1% DMSO or HDAC inhibitors in 1% DMSO for 16 h before total cell lysates were harvested for Western blot analysis using antibodies specific for p21. The amount of actin protein was also determined by Western blot as an indication for the sample loading on each lane of the gel.

oxime carboxylic acid **13** has been found to inhibit HDAC-1, with an IC_{50} of 200 nM.

Aryl-Aliphatic Chain Connection. To assess the importance or restriction of an aryl-aliphatic chain connection in HDAC-1 inhibition, several other functional groups such as an oxime (**9**), an exo methylene (**10**), and an internal alkene (**18**) were introduced in place of the ketone. Interestingly, such modifications do not affect enzyme inhibitory activity (cf. **8m** vs **9a**, **10**, **18**, and **8n** vs **9b**). However, 8-(2-naphthyl)octanoyl hydroxamic acid (**19**) or the corresponding secondary alcohol (**20**) have lower enzymatic inhibitory activity (cf. **8m** vs **19** and **20**). These results suggest that an sp^2 center at this junction may allow the inhibitor better interaction at the rim of the active site by forming an appropriate 110° angle between the adjacent aryl group and the aliphatic side chain.

Finally, introduction of an α-methyl group adjacent to the hydroxamate moiety resulted in a considerable decrease of HDAC inhibitory activity. The α-methylated derivative **16** (IC_{50} = 600 nM) is 120 times less potent than the corresponding unsubstituted compound **8m** (IC_{50} = 5 nM). This result demonstrates that even a small group may not be tolerable near the zinc binding site of HDAC-1, and this is in good agreement with the proposed tubelike narrow active site pocket of HDAC.[10a]

HDAC Inhibitors in Cell-Based Assays. To confirm the ability of our hydroxamates to inhibit HDAC in cells, we chose **8m**,**n**, **12**, and **15b** to evaluate the induction of histone acetylation in human bladder T24 cancer cells. Three compounds (**8n**, **12**, and **15b**) caused histone hyperacetylation in human cancer cells in a dose-dependent manner (Figure 1). The ability of these four compounds to induce histone acetylation in cells correlated largely with their enzyme inhibitory activities against HDAC-1 in vitro, with the exception that the naphthyl derivative **8m** induced histone acetylation in cells weakly. The *p*-bromobiphenyl compound **12** was the most effective, being as potent as TSA on induction of histone acetylation in human cancer T24 cells.

We also evaluated the in vitro antiproliferative activities of all of the above compounds using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assays against eight various human cancer cell lines (T24, HCT116, SW48, A549, H446, Du145, MDAmb231, and MCF-7) and a normal human epithelial cell line (HMEC). All compounds exhibit antiproliferative activities against human cancer cells with varying degrees of potency. Among them, compound **12** had the most potent antiproliferative activities against various human cancer cells, with IC_{50} values ranging from 0.05 to 3 μM. In contrast, compound **8m** was the weakest on growth inhibition of cancer cells, with IC_{50} values ranging from 1 to 30 μM. Compounds **12**, **15b**, and TSA showed selective growth inhibition of human cancer cells over human normal cells. However, compounds **8m**,**n** showed no evidence of selective growth inhibition (Table 2).

Similar to other known HDAC inhibitors, all four of the above compounds induced p21 protein expression in T24 human cancer cells. Their abilities to induce p21 correlated well with their abilities to induce histone acetylation, with the order of potency being **12** > **8n** > **15b** ≫ **8m** (Figure 2). Likewise, compounds **12**, **8n**, and **15b** induced both G1 and G2/M cell cycle arrests at concentrations equal to or less than 5 μM in human cancer cells (data not shown).

In summary, we have designed and synthesized a series of structurally simple TSA-like straight chain hydroxamates. Several of these new compounds were as potent as TSA in inhibiting HDAC-1 and were capable of inducing histone acetylation, inducing expression of p21, and causing cell cycle arrest and inhibition of cell proliferation. The SAR obtained in this study may aid in designing nonhydroxamate inhibitors of HDAC.

Experimental Section

Chemistry. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian 300 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to solvent peaks. Mass spectra were obtained on a HP1100 MSD instrument. Elemental analyses were within ±0.4% of calculated values. All reactions were run under a positive pressure of nitrogen unless otherwise stated. Flash

column chromatography was performed with silica gel 60 (230−400 mesh). Analytical high-performance liquid chromatography (HPLC) was performed on a HP1100 instrument equipped with a Zorbax (50 mm × 4.6 mm) C-8 column. The mobile phases used were as follows: A, H_2O with 0.01 M ethylenediaminetetraacetic acid (EDTA) + formic acid to pH 5; B, MeOH with 0.05% formic acid, using a solvent gradient of A/B 20/80 to 95/5. The analyses were performed at 25 °C with a constant flow rate of 1 mL/min using a gradient elution of 0−10 min.

Preparation of Organocopper Reagent (6). To a suspension of zinc foil (3.40 g, 52 mmol) in tetrahydrofuran (THF, 4 mL) was added 1,2-dibromoethane (0.38 g, 2.0 mmol), and the mixture was heated to 65 °C for 1 min. After it was cooled to room temperature, chlorotrimethylsilane (0.2 mL, 1.6 mmol) was added, and the mixture was stirred for 15 min. A solution of ethyl 7-iodoheptanoate (14.21 g, 50 mmol) in THF (20 mL) was added slowly at room temperature, and the mixture was heated to 60 °C for 16 h and then cooled to −10 °C. To this, a solution of CuCN (3.96 g, 44 mmol) and anhydrous LiCl (3.80 g, 88 mmol) in THF (44 mL) was added via cannula. The resulting solution was stirred at 0 °C for 10 min and then used for the coupling reactions with various acid chlorides.

General Procedure for Conversion of 6 to 8. Ethyl 7-benzoylheptanoate (7c). To a stirring solution of organocopper reagent **6** (2.0 mmol) in THF (4 mL) at −25 °C was added benzoyl chloride (253 mg, 0.21 mmol), and the reaction mixture was warmed to 0 °C over 30 min. After it was stirred for an additional 3 h at 0 °C, the reaction mixture was quenched with a saturated NH_4Cl solution and then extracted with ethyl acetate. The combined organic extracts were washed with brine, dried, and concentrated under reduced pressure. The crude product was purified by flash chromatography (10% ethyl acetate in hexanes) to afford the title compound **7c** (Ar = phenyl) (376 mg, 80% yield). ^{1}H NMR ($CDCl_3$): δ 7.42−7.97 (m, 5H), 4.12 (q, J = 6.9 Hz, 2H), 2.97 (t, J = 7.2 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.74 (m, 2H), 1.65 (m, 2H), 1.39 (m, 4H), 1.25 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 14.19, 24.04, 24.75, 28.90 (2), 34.12, 38.39, 60.11, 127.96, 128.49, 132.84, 136.95, 173.70, 200.29.

***N*-Hydroxy-7-benzoylheptanamide (8c).** To a stirring solution of **7c** (Ar = phenyl) (610 mg, 2.3 mmol) in THF (3.5 mL) and MeOH (3.5 mL) at room temperature was added 1 N NaOH (3.5 mL, 3.5 mmol), and the mixture was stirred for 2 h. After organic solvents were removed, the resulting aqueous solution was acidified with 1 N HCl and then extracted with ethyl acetate. The combined organic layers were dried and then concentrated under reduced pressure to give the crude product. Purification by flash chromatography (7% methanol in chloroform) afforded 7-benzoyl heptanoic acid (511 mg, 94% yield) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.96 (d, J = 6.9 Hz, 2H), 7.41−7.61 (m, 3H), 2.97 (t, J = 7.5 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 1.75 (m, 2H), 1.66 (m, 2H), 1.40 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 24.01, 24.43, 28.80, 28.86, 33.92, 38.37, 127.98, 128.50, 132.88, 136.91, 179.95, 200.44.

To a stirring solution of 7-benzoyl heptanoic acid (200 mg, 0.85 mmol) at room temperature in anhydrous dimethylformamide (DMF, 5 mL) was added 1-hydroxybenzotriazole hydrate (149 mg, 1.11 mmol) followed by 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (191 mg, 1.28 mmol). After 1 h, hydroxylamine hydrochloride (66 mg, 0.94 mmol) and Et_3N (130 μL, 0.94 mmol) were added, and stirring was continued at room temperature overnight. The solvent was removed in vacuo, and the residue was diluted with ethyl acetate and then was washed with saturated aqueous $NaHCO_3$. After it was dried and concentrated, the crude product was purified by flash chromatography (2−10% methanol in chloroform) to give **8c** (98 mg, 46% yield). ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.95 (d, J = 7.2 Hz, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 2.98 (d, J = 7.5 Hz, 2H), 2.13 (m, 2H), 1.72 (m, 2H), 1.64 (m, 2H), 1.38 (m, 4H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 23.77, 24.98, 28.49 (2), 32.49, 38.13, 127.73, 128.29, 132.86, 136.46, 171.23, 201.16. Anal. ($C_{14}H_{19}NO_3$) C, H, N.

Compounds **8a**,**b**,**d**−**n** were all prepared in a manner similar or identical to that described for compound **8c**.

***N*-Hydroxy-5-(benzoyl)pentanamide (8a).** ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.86 (d, J = 6.9 Hz, 2H), 7.59−7.43 (m, 3H), 3.01 (br t, 2H), 2.18 (br t, 2H), 1.72 (m, 4H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 23.24, 24.78, 32.39, 37.79, 127.76, 128.36, 133.00, 136.38, 170.85, 200.82. Anal. ($C_{12}H_{15}NO_3$) C, H, N.

***N*-Hydroxy-6-(benzoyl)hexanamide (8b).** ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.94 (d, J = 7.5 Hz, 2H), 7.61−7.40 (m, 3H), 2.98 (t, J = 6.9 Hz, 2H), 2.15 (t, J = 6.6 Hz, 2H), 1.80−1.60 (m, 4H), 1.41 (m, 2H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 23.48, 25.04, 28.37, 32.39, 38.08, 127.87, 128.45, 133.03, 136.57, 171.16, 201.05. Anal. ($C_{13}H_{17}NO_3$) C, H, N.

***N*-Hydroxy-8-(benzoyl)octanamide (8d).** ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.86 (d, J = 7.5 Hz, 2H), 7.51−7.35 (m, 3H), 2.89 (t, J = 6.9 Hz, 2H), 2.02 (t, J = 6.6 Hz, 2H), 1.70−1.45 (m, 4H), 1.26 (m, 6H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 23.95, 25.15, 28.59, 28.74, 288.78, 32.55, 38.27, 127.79, 128.36, 132.91, 136.55, 171.27, 201.32. Anal. ($C_{15}H_{21}NO_3$) C, H, N.

***N*-Hydroxy-6-(4-methoxybenzoyl)hexanamide (8e).** ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.86 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H), 2.87 (t, J = 6.6 Hz, 2H), 2.07 (br t, 2H), 1.62 (m, 4H), 1.34 (m, 2H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 23.68, 24.96, 28.32, 32.28, 37.63, 55.14, 113.49, 129.48, 130.13, 163.35, 171.06, 199.81. Anal. ($C_{14}H_{19}NO_4$) C, H, N.

***N*-Hydroxy-6-(2-naphthoyl)hexanamide (8f).** ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 8.47 (s, 1H), 8.05−7.50 (m, 6H), 3.12 (br t, 2H), 2.15 (br t, 2H), 1.82−1.60 (m, 4H), 1.46 (m, 2H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 23.59, 25.02, 28.36, 32.33, 38.06, 123.40, 126.56, 127.46, 128.21, 128.29, 129.29, 129.60, 132.25, 133.78, 135.37, 171.04, 201.04. Anal. ($C_{17}H_{19}NO_3$) C, H, N.

***N*-Hydroxy-7-(2-thiophene)carbonylheptanamide (8h).** ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.76 (d, J = 2.7 Hz, 1H), 7.68 (d, J = 4.5 Hz, 1H), 7.16 (m, 1H), 2.92 (d, J = 7.5 Hz, 2H), 2.10 (t, J = 7.5 Hz, 2H), 1.74 (m, 2H), 1.64 (m, 2H), 1.36 (m, 4H). Anal. ($C_{12}H_{17}NO_3S$) C, H, N.

***N*-Hydroxy-7-(2-methoxybenzoyl)heptanamide (8i).** ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.81 (dd, J = 8.1, 1.8 Hz, 1H), 7.47 (m, 1H), 7.02−6.97 (m, 2H), 3.90 (s, 3H), 2.97 (t, J = 7.2 Hz, 2H), 2.10 (t, J = 7.2 Hz, 2H), 1.74−1.56 (m, 4H), 1.36 (m, 4H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 23.89, 25.05, 28.68, 28.60, 32.50, 43.28, 55.17, 111.35, 120.33, 128.03, 129.69, 133.26, 158.18, 171.18, 204.09. Anal. ($C_{15}H_{21}NO_4$) C, H, N.

***N*-Hydroxy-7-(*p*-anisoyl)heptanamide (8j).** ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.94 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 3.88 (s, 3H), 2.93 (t, J = 7.2 Hz, 2H), 2.11 (t, J = 7.5 Hz, 2H), 1.59−1.79 (m, 4H), 1.37 (m, 4H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 24.15, 25.04, 28.59 (2), 32.51, 37.88, 55.21, 113.54, 129.58, 130.20, 163.39, 171.10, 200.06. Anal. ($C_{15}H_{21}NO_4$) C, H, N.

***N*-Hydroxy-7-(4-trifluoromethylbenzoyl)heptanamide (8k).** ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 8.07 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 3.02 (t, J = 7.5 Hz, 2H), 2.12 (t, J = 7.5 Hz, 2H), 1.75 (m, 2H), 1.65 (m, 2H), 1.40 (m, 4H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 23.57, 25.03, 28.51, 28.59, 32.50, 38.50, 123.37 (q, J_{CF} = 273 z), 125.43 (q, J_{CF} = 3.7 Hz), 128.18, 134.09 (q, J_{CF} = 32.6 Hz), 139.32, 171.15, 199.93. Anal. ($C_{15}H_{18}F_3NO_3$) C, H, N.

***N*-Hydroxy-7-(4-bromobenzoyl)heptanamide (8l).** ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.82 (d, J = 7.5 Hz, 2H), 7.62 (d, J = 7.5 Hz, 2H), 2.95 (t, J = 7.2 Hz, 2H), 2.11 (m, 2H), 1.55−1.79 (m, 4H), 1.38 (m, 4H). Anal. ($C_{14}H_{18}BrNO_3$) C, H, N.

***N*-Hydroxy-7-(2-naphthoyl)heptanamide (8m).** ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 8.47 (s, 1H), 7.53−8.01 (m, 6H), 3.10 (t, J = 7.5 Hz, 2H), 2.12 (m, 2H), 1.78 (m, 2H), 1.66 (m, 2H), 1.42 (m, 4H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 24.01, 25.07, 28.62(2), 32.54, 38.27, 123.47, 126.56, 127.48, 128.22, 128.28, 129.03, 129.60, 132.27, 133.86, 135.37, 171.19, 201.18. Anal. ($C_{18}H_{21}NO_3$) C, H, N.

***N*-Hydroxy-7-[(4-biphenyl)carbonyl]heptanamide (8n).** ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 8.03 (d, J = 7.8 Hz, 2H), 7.70 (d, J = 7.8 Hz, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.55−7.38 (m, 3H), 3.02 (t, J = 6.9 Hz, 2H), 2.12 (t, J = 7.2 Hz, 2H), 1.75 (m, 2H), 1.66 (m, 2H), 1.41 (m, 4H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 23.96, 25.06, 28.61(2), 32.54, 38.29, 126.98, 127.02, 128.02, 128.47, 128.71, 135.26, 139.55, 145.66, 171.09, 200.92. Anal. ($C_{20}H_{23}NO_3$) C, H, N.

***N*-Hydroxy-7-[(3-pyridyl)carbonyl]heptanamide (8g). (i) Methyl-7-[3-(pyridyl)carbonyl]heptanoate (7g).** To a stirring solution of 3-bromopyridine (1.58 g, 10 mmol) in anhydrous ethyl ether (100 mL) at −78 °C was added *n*-butyllithium (1.6 M in hexane, 7.5 mL), and the resulting solution was stirred at −78 °C for 10 min. Trimethyltin chloride (2.39 g, 12 mmol) was added, and the mixture was stirred at −78 °C for 20 min and then warmed to room temperature over 1 h. The reaction mixture was diluted with hexanes (30 mL) and washed with water. The organic phase was dried and concentrated to provide the crude product, which was purified by vacuum distillation (125 °C at 15−20 mm Hg) to give 3-trimethylstannyl pyridine (1.93 g, 80% yield).

A mixture of 3-trimethylstannyl pyridine prepared above (1.89 g, 7.81 mmol) and methyl 8-chloro-8-oxooctanoate in benzene (20 mL) was heated overnight at reflux in the presence of $PdCl_2(PPh_3)_2$ (274 mg, 0.39 mmol). After it was cooled to room temperature, the reaction mixture was partitioned between ethyl acetate and water. The combined organic layers were dried and concentrated. Purification by flash chromatography (50% ethyl acetate in hexane) yielded the desired product **7g** (Ar = 3-pyridyl) (1.15 g, 59% yield) as a light yellow solid. ^{1}H NMR (CD_3OD): δ 9.16 (d, J = 1.8 Hz, 1H), 8.77 (dd, J = 4.8, 1.8 Hz, 1H), 8.23 (m, 1H), 7.43 (dd, J = 7.8, 4.8 Hz, 1H), 3.67 (s, 3H), 2.99(t, J = 7.5 Hz, 2H), 2.32 (t, J = 7.5 Hz, 2H), 1.77 (m, 2H), 1.65 (m, 2H), 1.41 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 23.66, 24.66, 28.78, 28.84, 33.89, 38.67, 51.41, 123.58, 132.11, 135.27, 149.54, 153.31, 174.06, 198.96.

(ii) *N*-Hydroxy-7-[3-(pyridyl)carbonyl]heptanamide (8g). Compound **8g** was prepared from **7g** (Ar = 3-pyridyl) in an identical manner to that described for compound **8c**. ^{1}H NMR (20% CD_3OD in CD_3OD): δ 9.12 (d, J = 1.5 Hz, 1H), 8.74 (dd, J = 4.8, 1.5 Hz, 1H), 8.30 (m, 1H), 7.50 (dd, J = 7.8, 4.8 Hz, 1H), 3.02 (t, J = 7.5 Hz, 2H), 2.12 (t, J = 7.5 Hz, 2H), 1.75 (m, 2H), 1.65 (m, 2H), 1.40 (m, 4H). ^{13}C NMR (20% CD_3OD in CD_3OD): δ 23.39, 25.00, 28.44, 28.53, 32.48, 38.46, 123.86, 132.17, 135.80, 148.83, 152.61, 171.06, 199.31. Anal. ($C_{13}H_{18}N_2O_3$) C, H, N.

***N*-Hydroxy-8-(*E*)-oximino-8-(2-naphthyl)octanamide (9a).** Following the procedure described above for compound **8c**, but using 5 equiv of $NH_2OH{\cdot}HCl$ and triethylamine each, to afford **9a** from the corresponding carboxylic acid in 40% yield. ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 8.00 (s, 1H), 7.90−7.40 (m, 6H), 2.91 (t, J = 7.2 Hz, 2H), 2.07 (t, J = 6.9 Hz, 2H), 1.61 (m, 4H), 1.38 (m, 4H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 25.03, 25.46, 25.86, 28.37, 28.92, 32.39, 123.43, 125.38, 125.90, 126.08, 127.15, 127.60, 127.94, 132.79, 133.14, 133.17, 159.01, 171.17. Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

***N*-Hydroxy-8-(*E*)-oximino-8-(4-biphenyl)octanamide (9b).** Following the procedure described above for compound **8c**, but using 5 equiv of $NH_2OH{\cdot}HCl$ and triethylamine each, to afford **9b** from the corresponding carboxylic acid in 45% yield. ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.25−7.67 (m, 9H), 7.36 (m, 3H), 2.82 (t, J = 7.5 Hz, 2H), 2.06 (br t, J = 6.9 Hz, 2H), 1.59 (m, 4H), 1.37 (m, 4H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 25.13, 25.78, 25.88, 28.47, 29.00, 32.58, 126.51, 126.72, 126.85, 127.33, 128.59, 134.72, 140.14, 141.47, 159.17, 171.24. Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

***N*-Hydroxy-8-(2-naphthyl)non-8-enamide (10). (i) Ethyl 8-(2-naphthyl)non-8-enoate.** To a solution of methyltriphenylphosphonium bromide (469 mg, 1.31 mmol) in THF (6 mL), precooled to 0 °C under nitrogen, was added *n*-butyllithium (1.42 M solution in hexanes, 905 μL, 1.28 mmol) dropwise. The mixture was stirred over 20 min. A solution of **7m** (Ar = 2-naphthyl) (82 mg, 0.262 mmol) in THF (4 mL) was added via cannula. The yellow mixture was stirred over 30 min and quenched with a saturated aqueous solution of NH_4Cl. The solvent was removed by evaporation in vacuo, and the aqueous residue was then extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by flash chromatography (5−8% diethyl ether in hexane) to afford the title compound (43 mg) in 52% yield. ^{1}H NMR ($CDCl_3$): δ 7.85−7.78 (m, 4H), 7.58 (dd, J = 8.8, 1.9 Hz, 1H), 7.48−7.44 (m, 2H), 5.42 (d, J = 1.1 Hz, 1H), 5.16 (d, J = 1.4 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.62 (t, J = 6.9 Hz, 2H), 2.28 (d, J = 7.4 Hz, 2H), 1.64−1.49 (m, 4H), 1.39−1.33 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H). LRMS (ESI) = 311 (MH^+).

(ii) *N*-Hydroxy-8-(2-naphthyl)non-8-enamide (10). The above compound was then transformed into **10** in a manner similar to that described for compound **8c**. ^{1}H NMR ($CDCl_3$): δ 8.22 (bs, 1H), 7.80−7.77 (m, 4H), 7.56 (d, J = 8.5 Hz, 1H), 7.46−7.44 (m, 2H), 5.39 (s, 1H), 5.13 (s, 1H), 2.59 (t, J = 6.6 Hz, 2H), 2.05 (bs, 2H), 1.56−1.11 (m, 8H). HRMS: calcd, 297.1729; found, 297.1744.

***N*-Hydroxy-7-[4-(4-bromophenyl)benzoyl]heptanamide (12). (i) Ethyl-7-[4-(4-bromophenyl)benzoyl]heptanoate (11).** To a mixture of 4-bromophenyl boronic acid (1.21 g, 6.0 mmol) and **7l** (Ar = 4-bromophenyl) (2.04 g, 6.0 mmol) were added toluene (70 mL) and ethanol (3 mL) followed by a 2 M Na_2CO_3 aqueous solution (6.3 mL, 12.6 mmol). The resulting mixture was degassed for 10 min, and then, $Pd(PPh_3)_4$ (0.35 g, 0.3 mmol) was added. After 16 h of reflux, the mixture was cooled to room temperature, filtered through a pad of Celite, and rinsed with ethyl acetate. The organic solution was washed with brine, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (10% methanol in dichloromethane) followed by crystallization from ethanol and chloroform afforded the ester **11** (Ar = 4-bromophenyl) (1.30 g, 52% yield). ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 8.02 (d, J = 8.7 Hz, 2H), 7.75−7.40 (m, 6H), 4.13 (q, J = 6.9 Hz, 2H), 3.01 (t, J = 6.9 Hz, 2H), 2.32 (t, J = 7.2 Hz, 2H), 1.75 (m, 2H), 1.66 (m, 2H), 1.41 (m, 4H), 1.26 (t, J = 6.9 Hz, 3H).

(ii) *N*-Hydroxy-7-[4-(4-bromophenyl)benzoyl]heptanamide (12). The above compound **11** (Ar = 4-bromophenyl) was then transformed into **12** in a manner similar to that described for compound **8c**. ^{1}H NMR (DMSO-d_6): δ 10.33 (s, 1H), 8.66 (s, 1H), 8.04−7.70 (m, 8H), 3.04 (m, 2H), 1.94 (m, 2H), 1.62 (m, 2H), 1.49 (m, 2H), 1.30 (m, 4H). ^{13}C NMR (DMSO-d_6): δ 23.72, 24.98, 28.43 (2), 32.23, 37.90, 121.93, 126.79, 128.64, 129.03, 131.96, 135.78, 138.07, 143.06, 169.06, 199.57. HRMS: calcd, 385.0677 ($M-H_2O$); found, 385.0685. Anal. ($C_{20}H_{22}BrNO_3$) C, H, N.

(*E*)-Oximino-8-(4-biphenyl)octanoic Acid (13). A mixture of 7-[4-(4-phenyl)benzoyl]heptanoic acid (53 mg, 0.171 mmol) and $NH_2OH{\cdot}HCl$ (60 mg, 0.854 mmol) was heated at 50 °C in pyridine (0.5 mL) overnight. After excess of pyridine was removed, the residue was taken up in water (5 mL), acidified with 1 N HCl (pH ca. 4), and extracted with ethyl acetate. The combined organic layers were dried and then concentrated under reduced pressure to give the crude product. Purification by flash chromatography (10% methanol in chloroform) afforded the title compound (50 mg, 89% yield) as a white solid. ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.35−7.68 (m, 9H), 2.83 (t, J = 7.8 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 1.62 (m, 2H), 1.60 (m, 2H), 1.40 (m, 4H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 24.55, 25.92, 28.58 (2), 29.29, 33.79, 126.52, 126.75, 126.86, 127.31, 128.58, 134.76, 140.17, 141.46, 159.20, 176.54. Anal. ($C_{20}H_{24}N_2O_3$) C, H, N.

***N*-Hydroxy-7-[4-(1-piperidinyl)benzoyl]heptanamide (15a). (i) Ethyl-7-[4-(1-piperidinyl)benzoyl]heptanoate (14a).** To a mixture of **7l** (Ar = 4-bromophenyl) (1.03 g, 3.02 mmol), $Pd_2(dba)_3$ (0.14 g, 0.15 mmol), (±)BINAP (0.28 g, 0.45 mmol), and Cs_2CO_3 (1.37 g, 4.2 mmol) dissolved in dry toluene (2 mL) was added piperidine (0.9 mL, 9.12 mmol). The mixture was degassed for 10 min by bubbling with a nitrogen stream and then heated to 100 °C for 24 h. After it was cooled to room temperature, the reaction mixture was partitioned between

ethyl acetate and water. The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by flash chromatography (25% ethyl acetate in hexanes) gave **14a** in 40% yield. ^{1}H NMR ($CDCl_3$): δ 7.81 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 4.07 (q, J = 7.2 Hz, 2H), 3.30 (m, 4H), 2.81 (t, J = 7.5 Hz, 2H), 2.24 (t, J = 7.5 Hz, 2H), 1.74−1.56 (m, 10H), 1.20 (m, 4H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 14.23, 24.32, 24.28, 24.81, 25.32, 28.97, 29.07, 34.28, 37.79, 48.58, 60.11, 113.26, 126.40, 130.13, 154.29, 173.77, 198.63.

(ii) *N*-Hydroxy-7-[4-(1-piperidinyl)benzoyl]heptanamide (15a). Following the procedure described above for compound **8c**, the 7-[4-(1-piperidinyl)benzoyl]heptanoic acid was obtained in 98% yield. ^{1}H NMR ($CDCl_3$): δ 7.84 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.0 Hz, 2H), 3.35 (m, 4H), 2.86 (t, J = 7.5 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 1.74−1.56 (m, 10H), 1.20 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 24.25, 24.46, 24.65, 25.24, 28.81, 28.97, 33.92, 37.71, 48.53, 113.24, 126.25, 130.17, 154.27, 179.53, 198.87.

Following the procedure described above for compound **8c**, compound **15a** was obtained in 45% yield. ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.71 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 3.23 (m, 4H), 2.74 (t, J = 7.2 Hz, 2H), 1.98 (t, J = 6.6 Hz, 2H), 1.54 (m, 10H), 1.24 (m, 4H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 24.00, 24.50 24.99(2), 28.49, 28.58, 32.43, 37.49, 48.23, 112.96, 125.55, 130.11, 154.25, 171.15, 199.72. Anal. ($C_{19}H_{28}N_2O_3$) C, H, N.

***N*-Hydroxy-7-[4-(1-(4-phenylpiperazinyl))benzoyl]heptanamide (15b).** Following the procedure described above for compound **15a** but using the 1-phenyl-piperidine, the compound **15b** was obtained in 12% yield over three steps. ^{1}H NMR (20% CD_3OD in $CDCl_3$): δ 7.79 (d, J = 8.7 Hz, 2H), 7.19 (m, 2H), 6.89−6.78 (m, 5H), 3.41 (m, 4H), 3.24 (m, 4H), 2.78 (t, J = 7.5 Hz, 2H), 2.00 (t, J = 7.5 Hz, 2H), 1.66−1.46 (m, 4H), 1.26 (m, 4H). ^{13}C NMR (20% CD_3OD in $CDCl_3$): δ 24.40, 25.03, 28.61 (2), 32.48, 37.65, 47.06, 48.96, 113.35, 116.24, 120.22, 126.89, 128.98, 130.06, 150.65, 153.89, 171.11, 199.86. Anal. ($C_{24}H_{31}N_3O_3$) C, H, N.

***N*-Hydroxy-2-methyl-7-(2-naphthoyl)heptanamide (16).**
(i) Ethyl-8-(2-naphthyl)-8-[2-(1,3-dioxolyl)]octanoate. To a solution of **7m** (Ar = 2-naphthyl) (4.52 g, 14.47 mmol) in dichloromethane (140 mL) was added ethylene glycol (8.07 mL, 144.7 mmol) followed by boron trifluoride etherate (3.67 mL, 28.94 mmol). The mixture was stirred for 1 h at room temperature. Then, trimethylorthoformate (2.73 mL, 21.71 mmol) was added and the mixture was stirred overnight. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate, and the layers were separated. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by flash chromatography (15−20% ethyl acetate/hexane) to afford the title compound in 44% yield. ^{1}H NMR ($CDCl_3$): δ 7.91 (s, 1H), 7.87−7.81 (m, 3H), 7.54 (dd, J = 8.5, 1.4 Hz, 1H), 7.49−7.46 (m, 2H), 4.12−4.03 (m, 4H), 3.82−3.78 (m, 2H), 2.23 (t, J = 7.4 Hz, 2H), 1.99−1.94 (m, 2H), 1.59−1.54 (m, 2H). LRMS (ESI) = 357 (MH^+).

(ii) Ethyl-2-methyl-8-(2-naphthyl)-8-[2-(1,3-dioxolyl)]-octanoate. To a solution of diisopropylamine (550 μL, 3.93 mmol) in THF (40 mL) cooled to 0 °C under nitrogen was added dropwise *n*-butyllithium (1.2 M solution in hexanes, 3.12 mL, 3.65 mmol). The mixture was stirred at 0 °C for 20 min and then cooled to −78 °C. A cooled (−78 °C) solution of the above ester (1.0 g, 2.81 mmol) in THF (15 mL) was transferred via cannula. The mixture was stirred for 1 h at −78 °C. Then, a cooled (−78 °C) solution of iodomethane (349 μL, 5.61 mmol) in THF (15 mL) was transferred via cannula. The resulting mixture was stirred at −78 °C for 30 min, quenched with saturated aqueous NH_4Cl, and then stirred for 4 h at room temperature. The mixture was concentrated in vacuo, and the aqueous residue was extracted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by flash chromatography (10% ethyl acetate in hexane) to afford the title compound (950 mg) in 91% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.87−7.81 (m, 3H), 7.54 (dd, J = 8.8, 1.9 Hz, 1H), 7.51−7.45 (m, 2H), 4.12−4.03 (m, 4H), 3.86−3.78 (m, 2H), 2.35 (sext, J = 7.1 Hz, 1H), 1.99−1.94 (m, 2H), 1.60−1.54 (m, 2H), 1.35−1.19 (m, 9H), 1.09 (d, J = 6.9 Hz, 3H). LRMS (ESI) = 371 (MH^+).

(iii) Ethyl-2-methyl-7-(2-naphthoyl)heptanoate. To a solution of the previous compound (950 mg, 2.56 mmol) in acetone (75 mL) was added 1 N HCl (15 mL) until a precipitate persisted, followed by acetone until a solution was obtained. The mixture was stirred at room temperature for 1 h and then at 50 °C for 1 h. The mixture was concentrated in vacuo to 10 mL. The white precipitate formed was filtered and rinsed with water to give the title compound. ^{1}H NMR ($CDCl_3$): δ 8.47 (s, 1H), 8.04−7.96 (m, 2H), 7.91−7.86 (m, 2H), 5.57 (quintd, J = 7.7, 1.9 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.09 (t, J = 7.4 Hz, 2H), 2.46−2.39 (m, 1H), 1.82−1.51 (m, 4H), 2.45−2.34 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H), 1.14 (d, J = 6.9 Hz, 3H). LRMS (ESI) = 327 (MH^+).

***N*-Hydroxy-2-methyl-7-(2-naphthoyl)heptanamide (16).** Following a procedure analogous to that described for compound **8c**, 2-methyl-7-(2-naphthoyl)heptanoic acid was obtained in 73% yield. ^{1}H NMR ($CDCl_3$): δ 8.47 (s, 1H), 8.03 (dd, J = 8.5, 1.6 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.57 (quintd, J = 7.7, 1.9 Hz, 2H), 3.10 (t, J = 7.1 Hz, 2H), 2.52−2.46 (m, 1H), 1.83−1.72 (m, 4H), 1.52−1.42 (m, 4H), 1.19 (d, J = 6.9 Hz, 3H). LRMS (ESI) = 299 (MH^+).

Following a procedure analogous to that described for compound **8c**, compound **16** was obtained in 65% yield. ^{1}H NMR ($CDCl_3$): δ 8.47 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.91−7.86 (m, 2H), 7.63−7.55 (m, 2H), 3.18−3.02 (m, 2H), 2.31−2.17 (m, 1H), 1.73−1.694 (m, 2H), 1.50−1.28 (m, 4H), 1.11−1.07 (m, 3H). HRMS: calcd, 313.1678; found, 313.1685.

***(E/Z)*-Ethyl 8-(2-naphthyl)-7-octenoate (17).** To a solution of ethyl 7-bromoheptanoate **5** (10.0 g, 42.17 mmol) in toluene (280 mL) was added triphenylphosphine (11.06 g, 42.17 mmol). The solution was refluxed over 24 h under nitrogen and then cooled to room temperature. The supernatant was transferred to a flask and an excess of triphenylphosphine (5.53 g, 21.09 mmol) was added. The solution was refluxed over 3 days and then cooled to room temperature without stirring to favor sedimentation. The supernatant was again removed by decantation, and the resulting colorless oil was dried under high vacuum affording (carbethoxyhexyl)triphenylphosphonium bromide (18.24 g) in 87% yield. ^{1}H NMR ($CDCl_3$): δ 7.96−7.62 (m, 9H), 7.37−7.08 (m, 6H), 4.11−4.00 (m, 2H), 3.86−3.70 (m, 2H), 2.37−2.32 (m, 4H), 2.28−2.19 (m, 2H), 1.72−1.46 (m, 6H), 1.31−1.25 (m, 2H), 1.22−1.15 (m, 3H). LRMS (ESI) = 419 (phosphonium ion).

To a suspension of the phosphonium salt (18.14 g, 36.32 mmol) in THF (300 mL) cooled to 0 °C was added *n*-butyllithium (1.13 M solution in hexanes, 35.4 mL, 39.95 mmol) dropwise. The resulting solution was stirred at 0 °C over 30 min, and a solution of 2-naphthaldehyde (5.67 g, 36.32 mmol) in THF (60 mL) was transferred dropwise via cannula. The mixture was stirred overnight at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic layers were successively washed with water and brine, dried over magnesium sulfate, and then concentrated in vacuo. The crude residue was purified by flash chromatography (6−8% ethyl acetate in hexane) to afford **17** in 34% yield as a mixture of *E* and *Z* isomers in ca. a 1:2 ratio. ^{1}H NMR ($CDCl_3$): δ 7.83−7.75 (m, 3H), 7.71 (s, 0.5H), 7.67 (s, 0.5H), 7.57 (dd, J = 8.5, 1.9 Hz, 0.5H), 7.49−7.38 (m, 2.5H), 6.57 (d, J = 11.5 Hz, 0.5H), 6.54 (d, J = 15.9 Hz, 0.5H), 6.34 (dt, J = 15.7, 7.1 Hz, 0.5H), 5.73 (dt, J = 11.8, 7.1 Hz, 0.5H), 4.17−4.10 (m, 2H), 2.42 (qd), J = 7.4, 1.9 Hz, 1H), 2.34−2.24 (m, 3H), 1.73−1.31 (m, 6H), 1.28−1.22 (m, 3H). LRMS (ESI) = 297 (MH^+).

***(E)*-*N*-Hydroxy-8-(2-naphthyl)-7-octenamide (18).** Following a procedure analogous to that described for compound **8c**, (*E*)-8-(2-naphthyl)-7-octenoic acid was obtained in 60% yield. ^{1}H NMR ($CDCl_3$): δ 7.79−7.75 (m, 3H), 7.67 (s, 1H), 7.57 (dd, J = 8.5, 1.7 Hz, 1H), 7.47−7.38 (m, 2H), 6.54 (d, J = 15.7

Hz, 1H), 6.34 (dt, J = 9.0, 6.6 Hz, 1H), 2.38 (t, J = 7.4 Hz, 2H), 2.28 (q, J = 6.6 Hz, 1H), 1.74−1.64 (m, 2H), 1.57−1.40 (m, 4H). LRMS (ESI) = 269 (MH^+).

Following a procedure analogous to that described for compound **8c**, **18** was obtained in 37% yield. ^{1}H NMR (CD_3OD): δ 7.79−7.74 (m, 3H), 7.67 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.45−7.36 (m, 2H), 6.56 (d, J = 15.7 Hz, 1H), 6.38 (dt, J = 15.7, 6.9 Hz, 1H), 2.28 (q, J = 6.3 Hz, 2H), 2.11 (t, J = 7.4 Hz, 2H), 1.72−1.62 (m, 2H), 1.58−1.50 (m, 2H), 1.46−1.40 (m, 2H). HRMS: calcd, 283.1572; found, 283.1567.

***N*-Hydroxy-8-(2-naphthyl)octanamide (19).** To a solution of **18** (30 mg, 0.106 mmol) in methanol (2 mL) was added a catalytic amount of 10% palladuim on charcoal. The mixture was degassed, placed under a hydrogen atmosphere, and stirred for 15 min. The mixture was filtered through a pad of Celite and rinsed with methanol. The filtrate was concentrated in vacuo to afford **19** (29.1 mg) in 97% yield. ^{1}H NMR (CD_3OD): δ 7.80−7.74 (m, 3H), 7.60 (s, 1H), 7.44−7.37 (m, 2H), 7.33 (dd, J = 8.2, 1.6 Hz, 1H), 2.77 (t, J = 7.4 Hz, 2H), 2.07 (t, J = 7.1 Hz, 2H), 1.71−1.64 (m, 2H), 1.62−1.57 (m, 2H), 1.37−1.28 (m, 6H). HRMS: calcd, 285.1729; found, 285.1727.

Synthesis of *N*-Hydroxy-8-hydroxy-8-(2-naphthyl)-2-octenamide (20). *O*-(*t*-Butyldimethylsilyl)-1-(2-naphthyl)-6-heptenol. A flame-dried round-bottomed flask was charged with magnesium turnings (1.23 g, 50.75 mmol). THF (70 mL) followed by 1,2-dibromoethane (381 mg, 2.03 mmol) were added under nitrogen. A solution of 6-bromohexene (8.28 g, 50.75 mmol) in THF (30 mL) was added via cannula, and the mixture was refluxed overnight. A solution of 2-naphthaldehyde (6.10 g, 39.04 mmol) in THF (30 mL) was transferred via cannula to the Grignard reagent precooled to −78 °C, and the mixture was slowly warmed to 0 °C over 3 h. After it was stirred at that temperature for an additional 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography (10−15% ethyl acetate in hexane) to afford 1-(2-naphthyl)-6-heptenol in 89% yield (8.33 g). ^{1}H NMR ($CDCl_3$): δ 7.85−7.78 (m, 4H), 7.51−7.44 (m, 3H), 5.85−5.72 (m, 1H), 5.02−4.91 (m, 2H), 4.87−4.82 (m, 2H), 2.08−2.01 (m, 2H), 1.94−1.80 (m, 2H), 1.53−1.23(m, 4H). LRMS (ESI) = 223 (MH^+-H_2O).

To a solution of the above alcohol (1.0 g, 4.16 mmol) in dichloromethane (40 mL) at room temperature under a nitrogen atmosphere were successively added *tert*-butyldimethylsilyl chloride (815 mg, 5.41 mmol), imidazole (340 mg, 4.99 mmol), and a catalytic amount of 2,6-(dimethylamino)-pyridine. The mixture was stirred for 1 h, and then, triethylamine (696 μL, 4.99 mmol) was added. After it was stirred for 2 days, the reaction was quenched with water, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed successively with 1 N HCl, saturated aqueous sodium bicarbonate, then brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by flash chromatography (hexanes) to afford the title compound in 84% yield (1.24 g). ^{1}H NMR ($CDCl_3$): δ 7.83−7.79 (m, 3H), 7.70 (s, 1H), 7.47−7.40 (m, 3H), 5.78 (ddt, J = 17.0, 10.4, 6.6 Hz, 1H), 5.85−5.71 (m, 2H), 4.79 (dd, J = 6.9, 4.9 Hz, 1H), 2.04−1.98 (m, 2H), 1.80−1.54 (m, 2H), 0.90 (s, 9H), 0.04 (s, 3H), − 0.14 (s, 3H). LRMS (ESI) = 223 (MH^+-TBSO).

Methyl-8-*t*-butyldimethylsilyloxy-8-(2-naphthyl)-2-octenoate. To a solution of the alkene (1.05 g, 3.23 mmol) in *tert*-butyl alcohol (50 mL) were successively added water (10 mL), sodium bicarbonate (2.71 g, 32.3 mmol), sodium periodate (4.15 g, 19.38 mmol), and osmium tetroxide (8 mg, 0.032 mmol). The mixture was stirred for 3 h and then quenched with a 10% aqueous solution of sodium thiosulfate. After 30 min, the white precipitate was filtered off and rinsed with diethyl ether. The filtrate was concentrated in vacuo. The residue was partitioned between diethyl ether and water. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed successively with a 10% aqueous solution of sodium thiosulfate, water, and then brine, dried ($MgSO_4$), and concentrated, yielding 6-*tert*-butyldimethylsilyloxy-6-(2-naphthyl) hexanal as a crude oil in 91% yield (1.05 g). ^{1}H NMR ($CDCl_3$): δ 9.73 (t, J = 1.9 Hz, 1H), 7.83−7.78 (m, 3H), 7.69 (s, 1H), 7.49−7.43 (m, 3H), 4.80 (t, J = 6.9 Hz, 1H), 2.39 (td, J = 7.1, 1.6 Hz, 2H), 1.81−1.55 (m, 4H), 1.43−1.25 (m, 2H) 0.90 (s, 9H), 0.04 (s, 3H), − 0.15 (s, 3H). LRMS (ESI) = 225 ($M^{+1}-TBSO$).

To a suspension of sodium hydride (60% in mineral oil, 177 mg, 4.42 mmol) in THF (25 mL) at room temperature under nitrogen was added dropwise methyl diethylphosphonoacetate (811 μL, 4.42 mmol). The resulting solution was stirred for 10 min while cooling to 0 °C. A solution of the crude aldehyde (1.05 g, 2.94 mmol) in THF (10 mL) was transferred via cannula. The resulting solution was stirred for 15 min at 0 °C and quenched with a saturated aqueous solution of NH_4Cl. THF was removed in vacuo, and the aqueous residue was partitioned between diethyl ether and water. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by flash chromatography (5% ethyl acetate/hexane) to afford the title compound in 63% yield (1.30 g). ^{1}H NMR ($CDCl_3$): δ 7.83−7.78 (m, 3H), 7.69 (s, 1H), 7.49−7.41 (m, 3H), 6.94 (dt, J = 15.4, 7.1 Hz, 1H), 5.79 (dt, J = 15.7, 1.1 Hz, 1H), 4.79 (dd, J = 7.1, 5.2 Hz, 1H), 3.71 (s, 3H), 2.16 (q, J = 7.4 Hz, 2H), 1.81−1.62 (m, 2H), 1.48−1.26 (m, 4H), 0.90 (s, 9H), 0.04 (s, 3H), −0.15 (s, 3H). LRMS (ESI) = 413 (MH^+).

8-*t*-Butyldimethylsilyloxy-8-(2-naphthyl)-2-octenoic Acid. Following a procedure analogous to that described for compound **8c**, the title compound was obtained in 100% yield. ^{1}H NMR ($CDCl_3$): δ 7.83−7.78 (m, 3H), 7.72 (s, 1H), 7.48−7.40 (m, 3H), 6.74 (dt, J = 15.4, 7.1 Hz, 1H), 5.78 (d, J = 15.4 Hz, 1H), 4.88−4.84 (m, 1H), 2.17−2.11 (m, 2H), 1.82−1.69 (m, 2H), 1.47−1.28 (m, 4H), 0.89 (s, 9H), 0.06 (s, 3H), −0.16 (s, 3H). LRMS (ESI) = 421 (M^++Na).

***N*-Hydroxy-8-*t*-butyldimethylsilyloxy-8-(2-naphthyl)-2-octenamide.** Following a procedure analogous to that described for compound **8c**, the title compound was obtained in 44% yield. ^{1}H NMR (CD_3OD): δ 7.83−7.72 (m, 4H), 7.48−7.40 (m, 3H), 6.77 (dt, J = 15.1, 7.1 Hz, 1H), 5.75 (d, J = 15.4 Hz, 1H), 4.91−4.79 (m, 1H), 2.18−2.14 (m, 2H), 1.79−1.68 (m, 2H), 1.48−1.39 (m, 2H), 1.28−1.21 (m, 2H), 0.89 (s, 9H), 0.06 (s, 3H), −0.16 (s, 3H). LRMS (ESI) = 436 (M^++Na).

***N*-Hydroxy-8-hydroxy-8-(2-naphthyl)-2-octenamide.** To a solution of the silyl ether (300 mg, 0.725 mmol) in THF (3 mL) at room temperature was added 1 N HCl (3 mL). The mixture was stirred for 3 h at 30 °C. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by flash chromatography (75−100% ethyl acetate in hexane) to afford the title compound in 33% yield (77 mg). ^{1}H NMR (CD_3OD): δ 7.87−7.71 (m, 4H), 7.52−7.40 (m, 3H), 6.77 (dt, J = 15.1, 6.9 Hz, 1H), 5.75 (d, J = 15.1 Hz, 1H), 4.76 (t, J = 6.9 Hz, 1H), 2.17−2.10 (m, 2H), 1.84−1.77 (m, 2H), 1.49−1.27 (m, 4H) 1.88−1.75 (m, 4H). LRMS (ESI) = 282 (M^+-OH), 322 (M^++Na).

***N*-Hydroxy-8-hydroxy-8-(2-naphthyl)octanamide (20).** To a solution of the alkene (20 mg, 0.067 mmol) in methanol (670 μL) was added sodium borohydride (2.5 mg, 0.067 mmol). The mixture was stirred for 15 min, and the solvent was evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography (6% methanol in dichloromethane) afforded **20** in 46% yield (9.1 mg). ^{1}H NMR (CD_3OD): δ 7.84−7.76 (m, 4H), 7.50−7.40 (m, 3H), 4.75 (t, J = 6.6 Hz, 1H), 2.05 (t, J = 7.4 Hz, 2H), 1.86−1.76 (m, 2H), 1.62−1.55 (m, 2H), 1.43−1.23 (m, 6H). HRMS: calcd, 283.1572 ($M-H_2O$); found, 283.1581.

Biological Assays. Production of Recombinant HDAC1 Enzyme. Human HDAC-1 cDNA was generated by RT-polymerase chain reaction (PCR) reactions using primers complementary to the 5′ and 3′ coding sequence of human HDAC1 gene (Genbank accession number U50079). Error-free HDAC1 cDNA was inserted either into the pcDNA3.1 vector

(Invitrogen) or into the pBlueBAC (Invitrogen) vector, both with Flag epitope tagged at the C terminus of the protein. Insect high five cells (Invitrogen) were used to produce recombinant HDAC1. HDAC1 recombinant enzymes were partially purified by a Q-Sepharose column (Pharmacia) followed by purification using a column with anti-Flag M2 affinity gels (Sigma), according to manufacturer's instructions.

HDAC Enzyme Assay. [^{3}H]-labeled acetylated histones were prepared in Jurkat-T cells as described[9] and used as HDAC enzyme substrates. The assay was performed as in the literature.[9] Briefly, small molecule inhibitors diluted in dimethyl sulfoxide (DMSO) at various concentrations were preincubated with recombinant HDAC1 enzyme for 30 min at 4 °C in buffer containing 40 mM Tris-Cl, pH 7.6, 20 mM EDTA, and 50% glycerol. At 37 °C, [^{3}H]-labeled acetylated histones were added into the reaction mixture. The incubation time for the HDAC1 enzyme reaction was 10 min. The reaction was stopped, and released [^{3}H] acetic acid was extracted and quantified by scintillation counting. The 50% inhibitory concentrations (IC_{50}) for inhibitors were determined by analyzing dose−response inhibition curves.

Western Blot Analysis. Whole cell extracts or acid extracted histones prepared from inhibitor-treated cells were analyzed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS−PAGE). Proteins were transferred on the PVDF membrane and probed with various primary antibodies. Primary antibodies were ordered from Santa Cruz Biotechnology except for acetylated H4 or acetylated H3 antibodies (Upstate Biotechnology) or antibodies against $p21^{WAF1/Cip1}$ (Transduction Laborotories). Horseradish peroxidase-conjugated secondary antibodies (Sigma) were used, and the enhanced chemiluminescence (ECL, Amersham) was followed for detection.

MTT Assay. Compounds at various concentrations were added to cells plated in 96 well plates. Cells were incubated for 72 h at 37 °C in 5% CO_2 incubator. MTT (Sigma) was added at a final concentration of 0.5 mg/mL and incubated with the cells for 4 h before an equal volume of solubilization buffer (50% *N*,*N*-dimethylformamide, 20% SDS, pH 4.7) was added onto cultured cells. After overnight incubation, solubilized dye was quantified by colorimetric reading at 570 nM using a reference at 630 nM. OD values were converted to cell numbers according to a standard growth curve of the relevant cell line. The concentration that reduces cell numbers to 50% of those of DMSO-treated cells is determined as MTT IC_{50}.

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